

22043

(FILE 'USPAT' ENTERED AT 13:38:39 ON 23 FEB 93)

E STRACKE, M?/IN

E LIOTTA, L?/IN

L1

14 S E4

E SCHIFFMANN, E?/IN

E KRUTZSCH, H?/IN

L2

1 S (AUTOTAXIN#)

L3

497399 S (120 OR 121 OR 122 OR 123 OR 124 OR 125 OR 126 OR 127 OR

12

L4

10055 S (000 OR KD OR KDA OR K DALTON# OR KILODALTON#)

L5

154 S L3(W)L4

L6

2772 S (MOTILITY OR GROWTH) (W) (FACTOR# OR PROTEIN#)

L7

10 S L5 AND L6

L8

8 S (A2058)

L9

1 S L5 AND L8

L10

1562 S (MELANOMA#)

L11

0 S L7 AND L10

L12

12 S L5 AND L10

L13

4 S (MOTILITY FACTOR)

L14

0 S L5 AND L13

L15

2 S L10 AND L13

=> d 1-2 cdt, ab

1. 5,132,315, Jul. 21, 1992, Therapeutic application of an anti-invasive compound; Elise C. Kohn, et al., 514/359, 648, 650; 548/257 [IMAGE AVAILABLE]

US PAT NO: 5,132,315 [IMAGE AVAILABLE]

L15: 1 of 2

ABSTRACT:

Tumor invasion and metastasis is the most life threatening aspect of cancer. Invasion and metastasis is a multistep process. Cellular functions required for invasion are attachment, locomotion and directed migration. Regulation of these processes may be independent of cell growth. A carboxylamino-imidazole compound was found to be potent inhibitor of tumor cell attachment, motility, invasion, proliferation, and metastasis. This compound and equivalents thereof constitute a cancer treatment agent of particular use in the treatment of peritoneal carcinomatosis of ovarian cancer.

2. 5,039,794, Aug. 13, 1991, Tumor egress factor and processes for producing the same; Marjorie L. Wier, et al., 530/399, 350, 351, 380, 395, 413, 414, 415, 416, 417 [IMAGE AVAILABLE]

US PAT NO: 5,039,794 [IMAGE AVAILABLE]

L15: 2 of 2

ABSTRACT:

A novel cell scattering factor, i.e., tumor egress factor (hereinafter "egressin") isolated from a clone derived from a human metastatic **melanoma** (M3827) which possesses a loose colony morphology and from a human monocytic cell line (U937) and processes for producing the same. Egressin is useful for the production of immunological reagents for the detection and treatment of metastatic lesions, for aiding in the transport of drugs across the blood-brain barrier, and for aiding in the control of the inflammatory response.

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human ovarian cancer, ovarian cancer, and SR-transformed rat embryo fibroblast cell lines were inhibited 60%-80% by 1-10 .mu.M L651582. I.p. injection of OVCAR-3 cells causes malignant ascites, peritoneal carcinomatosis, and serosal and visceral seeding that, if left untreated, are lethal to nude mice. I.p. L651582 markedly prolonged survival of nude mice heavily laden with ovarian cancer [mean survival time of treated group divided by mean survival time of control group = 220%]. The apparent mechanism of action of L651582 is via inhibition of the receptor-mediated stimulation of effector enzymes utilizing guanine nucleotide-binding protein signal transduction, which thus makes L651582 a novel anticancer agent.

L12 ANSWER 2 OF 7 COPYRIGHT 1993 ACS

CA112(13):112781t Autocrine ***motility*** ***factor*** stimulates a three-fold increase in inositol trisphosphate in human melanoma cells. Kohn, Elise C.; Liotta, Lance A.; Schiffmann, Elliott (Med. Branch, Natl. Cancer Inst., Bethesda, MD 20892, USA). Biochem. Biophys. Res. Commun., 166(2), 757-64 (Eng) 1990. CODEN: BBRC99. ISSN: 0006-291X.

AB The biochem. pathways through which tumor cell locomotion is mediated are poorly understood. Autocrine ***motility*** ***factor*** (AMF), which is produced by and stimulates motility in ***A2058*** human melanoma cells, was used to characterize phosphoinositide metab. activated in assocn. with tumor cell motility. AMF stimulated up to a 400% increase in de novo incorporation of [3H]-myo-inositol into cellular lipids beginning 40 min after exposure. In cells prelabeled with [3H]-myo-inositol, AMF stimulated a 200% increase in total inositol phosphates (inositol monophosphate, InsP1; inositol bisphosphate, InsP2; inositol trisphosphate, InsP3) after 90 min of exposure, with a 300% maximal increase in InsP3 at 120 min. InsP1 and InsP2 were maximally increased 130% of control values. Treatment with AMF stimulated a parallel dose-dependent increase in both motility and phosphoinositide metab. The ***A2058*** motile response to AMF is known to be inhibited markedly by cell pretreatment with pertussis toxin (PT). Inositol phosphate prodn. was inhibited by a 2-h pretreatment of cells with PT (0.5 .mu.g/mL). PT treatment of ***A2058*** membranes was assocd. with ADP-ribosylation of a 40-kDa protein, consistent with the presence of an .alpha. subunit of a guanine nucleotide-binding protein (G protein). Apparently, AMF elicits increases in cell motility and phosphoinositide metab. via a PT-sensitive G protein signal transduction pathway.

L12 ANSWER 3 OF 7 COPYRIGHT 1993 ACS

CA111(25):225947z The type I insulin-like growth factor is a motility receptor in human melanoma cells. Stracke, Mary L.; Engel, Jason D.; Wilson, Lori W.; Rechler, Matthew M.; Liotta, Lance A.; Schiffman, Elliott (Lab. Pathol., Natl. Cancer Inst., Bethesda, MD 20892, USA). J. Biol. Chem., 264(36), 21544-9 (Eng) 1989. CODEN: JBCHA3. ISSN: 0021-9258.

AB ***Insulin*** -like growth factors I and II (IGF-I and IGF-II) and insulin are chemotactic agents for the human ***melanoma*** ***cell*** line ***A2058***. The motility receptor mediating this response is the heterodimeric type I IGF receptor. These 3 factors are able to compete with 125I-labeled IGF-I for binding to the cell surface with IC50 values equal to .apprx.2 (IGF-I), .apprx.150 (IGF-II), and .apprx.300 nM (insulin). Crosslinking of 125I-labeled IGF-I to the cell surface with disuccinimidyl suberate followed by anal. with SDS-PAGE and autoradiog. reveals a 130-kilodalton (kDa) protein (reduced) consistent with the .alpha. component of a type I receptor and a 38-kDa protein which does not bind insulin, and thus could be another IGF-I cell surface binding protein. The anti-IGF-I receptor monoclonal antibody (.alpha.IR-3) also competes with labeled IGF-I in binding expts. In contrast, a

inhibits the motility induced by IGF-I, IGF-II, and insulin, pertussis toxin (0.01-1.0 .mu.g/mL) has no effect on the motility induced by the insulin-like growth factors or insulin on this cell line. Therefore, the type I IGF receptor appears to mediate a highly potent pertussis toxin-insensitive motility response to IGF-I, IGF-II, and insulin. In contrast, motility induced by the autocrine ***motility*** ***factor***, a cytokine produced by the A2058 cells, is not affected by .alpha.IR-3 but is extremely sensitive to pertussis toxin. When mixts. of autocrine motility factor and IGF-I are employed to induce chemotaxis, the resulting motility is greater than that induced by either agent alone. Evidently, motility in this melanoma cell line can be initiated through multiple receptors that stimulate the cells by sep. transduction pathways. This capability to respond to multiple stimuli could enhance the metastatic potential.

L12 ANSWER 4 OF 7 COPYRIGHT 1993 ACS

CA109(9):67690n Insulin-like growth factors stimulate chemotaxis in human melanoma cells. Stracke, Mary L.; Kohn, Elise C.; Aznavoorian, Sadie A.; Wilson, Lori L.; Salomon, David; Krutzsch, Henry C.; Liotta, Lance A.; Schiffmann, Elliott (Lab. Pathol., Natl. Cancer Inst., Bethesda, MD 20892, USA). Biochem. Biophys. Res. Commun., 153(3), 1076-83 (Eng) 1988. CODEN: BBRC9. ISSN: 0006-291X.

AB Insulin and insulin-like growth factors stimulate motility in the highly metastatic human melanoma cell line, ***A2058***. Insulin-like growth factor-I (IGF-I) is the most potent with a maximal response at 10 nM compared to the activities of insulin and insulin-like growth factor-II (IGF-II) which peak at 300-400 nM. Using checkerboard anal., the responses to IGF-I and insulin are predominantly chemotactic, although insulin had a chemokinetic component. Pertussis toxin does not inhibit the response to any of these polypeptides. However, in previous studies, the motile response to autocrine ***motility*** ***factor*** from these same ***A2058*** cells was markedly inhibited by pertussis toxin. 125I-labeled IGF-I binds saturably and specifically to the ***A2058*** cells. Scatchard anal. indicates a high binding affinity (dissocn. const. .apprx.3 .times. 10⁻¹⁰M) and an estd. 5000 receptors/cell. In addn. to their mitogenic properties, certain growth factors may profoundly enhance metastasis of tumor cells by their ability to induce motility.

L12 ANSWER 5 OF 7 COPYRIGHT 1993 ACS

CA108(11):92970r Autocrine ***motility*** ***factor*** (AMF) formation by cancer cells, its determination in cancer diagnosis, and AMF inhibitors for cancer treatment. Liotta, L. A.; Schiffmann, E. (United States Dept. of Health and Human Services, USA). U. S. Pat. Appl. US 58381 A0 1 Nov 1987, 30 pp. Avail. NTIS Order No. PAT-APPL-7-58381. (Eng). CODEN: XAXXAV. APPLICATION: US 87-58381 5 Jun 1987.

AB Autocrine ***motility*** ***factor*** (AMF), a peptide of mol. wt. .apprx.54,000 secreted by human breast carcinoma cells, stimulates random motility of tumor cells without affecting the migration of normal blood leukocytes. Its activity is inhibited by pertussis toxin. AMF showed both chemotactic (directional) and chemokinetic (randomly motile) activity on human melanoma ***A2058*** cells; the latter effect was .apprx.3-fold greater than the former. AMF had a unique N-terminal sequence. Its activity was partially blocked by cholera toxin, but was not blocked or substituted by known growth factors or serum factors. AMF was detd. in concd. urine samples in a microwell migration chamber assay with human MDA 435 cells with and without addn. of anti-AMF antibodies for detection of bladder carcinoma. The highest AMF levels were obsd. with the least differentiated tumors and with metastatic

CA107(13):110/69t Pertussis toxin inhibits stimulated motility independently of the adenylate cyclase pathway in human melanoma cells. Stracke, Mary L.; Guirguis, Raouf; Liotta, Lance A.; Schiffmann, Elliott (Lab. Pathol., Natl. Inst. Health, Bethesda, MD 20892, USA). Biochem. Biophys. Res. Commun., 146(1), 339-45 (Eng) 1987. CODEN: BBRC99. ISSN: 0006-291X.

AB The human melanoma cell line, ***A2058***, has previously been shown to respond to an autocrine ***motility*** ***factor***. Biochem. pathways that may be involved in the generation of such a motile response were studied. Pertussis toxin (PT) caused a profound, rapid decrease in stimulated motility that was dose- and time-dependent. Preincubation of cells for 2 h with .gtoreq.1 ng/mL PT significantly inhibited motility. A concn. of PT (0.5 .mu.g/mL) that completely eliminated migration after a 30 min preincubation had a markedly reduced effect when added 1 h after the start of the assay. In contrast, agents which selectively modulate or have a role in the adenylate cyclase pathway, e.g., cholera toxin, forskolin, the cAMP analog 8-bromoadenosine 3':5'-cyclic monophosphate, and the cyclase inhibitor 2',5'-dideoxyadenosine, all had negligible effect upon motility. These data are consistent with the presence of a receptor coupled to a PT-sensitive G protein initiating motility independently of the adenylate cyclase system.

CA105(7):58748c Tumor cell autocrine ***motility*** ***factor***. Liotta, Lance A.; Mandler, Raya; Murano, Genesio; Katz, David A.; Gordon, Richard K.; Chiang, Peter K.; Schiffmann, Elliott (Natl. Cancer Inst., Food Drug Adm., Bethesda, MD 20892, USA). Proc. Natl. Acad. Sci. U. S. A., 83(10), 3302-6 (Eng) 1986. CODEN: PNASA6. ISSN: 0027-8424.

AB A cell motility-stimulating factor has been isolated, purified, and partially characterized from the serum-free conditioned medium of human ***A2058*** melanoma cells. This activity was termed autocrine ***motility*** ***factor*** (AMF). AMF has the properties of a protein with an estd. size of 55 kilodaltons. At concns. .ltoreq.10 nM, AMF stimulated the random or directed motility of the producer cells. However, AMF was not an attractant for neutrophils. Amino acid anal. of the purified AMF protein revealed a high content of serine, glycine, glutamic acid, and aspartic acid residues. The activity of AMF was not replaced or blocked by known growth factors such as epidermal growth factor or type-B transforming growth factor. Mechanistic studies showed that AMF stimulated the incorporation of [3H]Me groups into cell membrane phospholipids after incubation with [Me-3H]methionine with a sustained increase in the methylation of phosphatidyl dimethylethanolamine to phosphatidylcholine. In contrast, AMF did not affect the incorporation of [1,2-14C]choline into phosphatidylcholine. AMF was produced in large amts. by 3 different clones of ras oncogene-transfected metastatic NIH 3T3 cells but not by the nontransformed parental cells. AMF may play a major role in the local invasive behavior of tumor cells and may also facilitate the concerted invasion by groups of tumor cells.

=> d cbib,

CA109(19):164814p Isolation and structural characterization of the human 4F2 heavy-chain gene, an inducible gene involved in T-lymphocyte activation. Gottesdiener, Keith M.; Karpinski, Beverly A.; Lindsten, Tullia; Strominger, Jack L.; Jones, Nancy H.; Thompson, Craig B.; Leiden, Jeffrey M. (Howard Hughes Med. Inst., Univ. Michigan, Ann Arbor, MI 48109, USA). Mol. Cell. Biol., 8(9), 3809-19 (Eng) 1988. CODEN: MCEBD4. ISSN: 0270-7306.

(FILE 'HOME' ENTERED AT 15:01:18 ON 23 FEB 93)

FILE 'REGISTRY' ENTERED AT 15:01:33 ON 23 FEB 93

L1 0 S DIEHLTSLDFFR/SQSP
L2 62 S YLNAT/SQSP
L3 8 S VLNYF/SQSP
L4 0 S L2 AND L3
L5 0 S (AUTOTAXIN)/CN

FILE 'CA' ENTERED AT 15:04:01 ON 23 FEB 93

L6 40 S L2
L7 6 S L3
L8 60 S (MOTILITY FACTOR#)/BI,AB
L9 0 S L6 AND L8
L10 0 S L7 AND L8
L11 48 S (A2058)/BI,AB
L12 7 S L8 AND L11
L13 0 S (AUTOTAXIN#)/BI,AB
L14 330070 S (120 OR 121 OR 122 OR 123 OR 124 OR 125 OR 126 OR 127 O
L15 249385 S (000 OR KD OR KDA OR K DALTON# OR KILODALTON#)/BI,AB
L16 7931 S L14(W)L15
L17 1 S L2 AND L16
L18 0 S L3 AND L16
L19 1 S L8 AND L16

=> d cbib

L19 ANSWER 1 OF 1 COPYRIGHT 1993 ACS

CA111(25):225947z The type I insulin-like growth factor is a motility receptor in human melanoma cells. Stracke, Mary L.; Engel, Jason D.; Wilson, Lori W.; Rechler, Matthew M.; Liotta, Lance A.; Schiffman, Elliott (Lab. Pathol., Natl. Cancer Inst., Bethesda, MD 20892, USA). J. Biol. Chem., 264(36), 21544-9 (Eng) 1989. CODEN: JBCHA3. ISSN: 0021-9258.

Q P 501 J 7

=> d 1-8 cbib

L29 ANSWER 1 OF 8 COPYRIGHT 1993 ACS

CA116(11):99483h Structural and biosynthetic characterization of the fibroblast ***growth*** ***factor*** receptor 3 (FGFR-3) protein. Keegan, Kathleen; Meyer, Suzanne; Hayman, Michael J. (Dep. Microbiol., State Univ. New York, Stony Brook, NY 11794, USA). Oncogene, 6(12), 2229-36 (Eng) 1991. CODEN: ONCNE5. ISSN: 0950-9232.

L29 ANSWER 2 OF 8 COPYRIGHT 1993 ACS

CA115(25):271071q Basic fibroblast ***growth*** ***factor*** induces 3T3 fibroblasts to synthesize and secrete a cyclophilin-like protein and .beta.2 microglobulin. Davis, Thomas R.; Tabatabai, Louisa; Bruns, Kerry; Hamilton, Richard T.; Nilsen-Hamilton, Marit (Dep. Biochem. Biophys., Iowa State Univ., Ames, IA 50011-3113, USA). Biochim. Biophys. Acta, 1095(2), 145-52 (Eng) 1991. CODEN: BBACAQ. ISSN: 0006-3002.

L29 ANSWER 3 OF 8 COPYRIGHT 1993 ACS

CA114(5):36605n Enhanced EGF mitogenic response is associated with enhanced tyrosine phosphorylation of specific cellular proteins in fibroblasts overexpressing c-src. Wilson, Linda K.; Parsons, Sarah J. (Mol. Biol. Inst., Univ. Virginia, Charlottesville, VA 22908, USA). Oncogene, 5(10), 1471-80 (Eng) 1990. CODEN: ONCNE5. ISSN: 0950-9232.

L29 ANSWER 4 OF 8 COPYRIGHT 1993 ACS

...growth... receptors on human vesicular tissue
by biochemical and immunohistochemical techniques. Stubbs, S. C.;
Hargreave, T. B.; Habib, F. K. (Univ. Dep. Surg., West. Gen. Hosp.,
Edinburgh EH4 2XU, UK). J. Endocrinol., 125(3), 485-92, 2 plates
(Eng) 1990. CODEN: JOENAK. ISSN: 0022-0795.

L29 ANSWER 5 OF 8 COPYRIGHT 1993 ACS

CA111(21):188245w Epidermal ***growth*** ***factor*** -induced
truncation of the epidermal ***growth*** ***factor***
receptor. Decker, Stuart J. (Rockefeller Univ., New York, NY 10021,
USA). J. Biol. Chem., 264(30), 17641-4 (Eng) 1989. CODEN: JBCHA3.
ISSN: 0021-9258.

L29 ANSWER 6 OF 8 COPYRIGHT 1993 ACS

CA111(11):90647d Detection of glucocorticoid sensitive secretory
proteins from human melanoma cells. DiSorbo, Dennis M. (W. Alton
Jones Cell Sci. Cent., Lake Placid, NY 12946, USA). In Vitro Cell.
Dev. Biol., 25(6), 557-63 (Eng) 1989. CODEN: ICDBEO. ISSN:
0883-8364.

L29 ANSWER 7 OF 8 COPYRIGHT 1993 ACS

CA110(1):6050c Identification and subcellular localization of proteins
that are rapidly phosphorylated in tyrosine in response to
colony-stimulating factor 1. Sengupta, A.; Liu, Wan Kyng; Yeung, Y.
G.; Yeung, D. C. Y.; Frackelton, A. Raymond, Jr.; Stanley, E.
Richard (Dep. Dev. Biol. Cancer, Albert Einstein Coll. Med., Bronx,
NY 10461, USA). Proc. Natl. Acad. Sci. U. S. A., 85(21), 8062-6
(Eng) 1988. CODEN: PNASA6. ISSN: 0027-8424.

L29 ANSWER 8 OF 8 COPYRIGHT 1993 ACS

CA101(15):123807e Production of EGF-containing polypeptides in Xenopus
oocytes microinjected with submaxillary gland mRNA. Burmeister,
Margit; Avivi, Aaron; Schlessinger, Joseph; Soreq, Hermona (Dep.
Chem. Immunol., Weizmann Inst. Sci., Rehovot, Israel). EMBO J.,
3(7), 1499-505 (Eng) 1984. CODEN: EMJOD6. ISSN: 0261-4189.

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(FILE 'HOME' ENTERED AT 15:01:18 ON 23 FEB 93)

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L1 0 S DIEHL7SLDFFR/SQSP
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L6 40 S L2
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L14 330070 S (120 OR 121 OR 122 OR 123 OR 124 OR 125 OR 126 OR 127 O
L15 249385 S (000 OR KD OR KDA OR K DALTON# OR KILODALTON#)/BI,AB
L16 7931 S L14(W)L15
L17 1 S L2 AND L16
L18 0 S L3 AND L16
L19 1 S L8 AND L16
L20 31402 S (GROWTH FACTOR#)/BI,AB
L21 227 S L20 AND L16
L22 48 S (A2058)/BI,AB

L25	6 S L23 AND L21
L26	1 S L19 OR L24
L27	76 S (125) (W) (000 OR KD OR KDA OR K DALON# OR KILODALTON#) / B
L28	0 S L8 AND L27
L29	8 S L20 AND L27

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COST IN U.S. DOLLARS

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TOTAL

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FULL ESTIMATED COST

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185.26

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

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